Remarks

Claims 21, 23-25 and 27-52 are pending in the subject application. Applicants acknowledge that claims 35-50 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claim 21, canceled claims 35-50 and added new claims 53 and 54. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 21, 23-25, 27-34, and 51-54 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 21, 23-25, 27-34, 51 and 52 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The Office Action indicates that it is not clear if the "biological preparation" initially contains gamma delta T lymphocytes and the method is intended to enrich the proportion of gamma delta T lymphocytes within the biological preparation, or if the biological preparation may contain any mononuclear cell population, and the method is intended to involve transdifferentiation of various (non-gamma delta T lymphocytes) mononuclear cells into gamma delta T lymphocytes. In response, Applicants respectfully assert that the claims as filed are definite; however, in the interest of expediting prosecution in this matter, the phrase "biological preparation" has been deleted from the claims and reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 21, 23-25, 27-34, 51 and 52 are rejected under 35 U.S.C. § 103(a) as obvious over Belmant *et al.* (U.S. Patent No. 6,660,723), in view of Skea *et al.* (2001), Garcia *et al.* (1998) and Valeri (1976). Belmant *et al.* is said to teach a method for enriching the concentration of gamma delta T lymphocytes in a cell sample, comprising providing a biological preparation comprising gamma delta T lymphocytes, and culturing the biological preparation with a phosphohalohydrin and interleukin-2. The Office Action states that with regards to the concentration of the IL-2 provided in the culture, while Belmant *et al.* disclose using 50 U/mL of IL-2, it is submitted that the concentration of the cytokines was recognized as a result effective variable that would have been routinely optimized by the artisan of ordinary skill. Applicants respectfully assert that the claimed invention is not obvious over the cited references. In particular, Applicants respectfully disagree with

the Examiner that the concentration of the cytokines would have been routinely optimized by the artisan of ordinary skill.

In this case, Applicants submit that the previous Office Actions have failed to establish that either IL-2 or IL-15 is a parameter art recognized to be a result effective parameter for the culture of γδ T-cells. As the Patent Office is aware, in order to assert that the concentration of either cytokine is a parameter that can be optimized by routine experimentation, it is required first that the concentration is recognized in the prior art as a result-effective variable. *See* MPEP 2144.05. Moreover, even if the prior art recognizes a variable as result-effective over a certain range, it may be that the prior art does not recognize the variable as result-effective over all ranges.

In the *Aller* case cited in the Office Action, for example, the court recognizes that temperature and acid concentration in general are variables that a chemist might optimize. However, the court goes out of its way to establish that at least one *claimed* combination of temperature and acid concentration would have been an attractive target to try (*see Aller* at 457-58 (bridging paragraph) (arguing that a skilled chemist would have expected a possible increase in reaction rate over the prior art of record for the claimed combination of 80 °C and 70% sulfuric acid)). In other words, the court makes a point of establishing that there was an art-supported reason that made it desirable to test the claimed reaction conditions. *See also* KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007) ("Often, it will be necessary for a court to look to [many different sources], all in order to determine whether there was an apparent reason to combine the known elements *in the fashion claimed* by the patent at issue") (emphasis added).

The Board of Patent Appeals and the predecessor of the Court of Appeals for the Federal Circuit (the Court of Customs and Patent Appeals) have held that while it may generally be a matter of obviousness for the skilled artisan to determine the optimum value within an already disclosed range, *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980), it would not have been obvious for one of ordinary skill in the art to find an optimum value that is far outside the range taught by the prior art. *See In re Sebek*, 465 F.2d 904, 907 (C.C.P.A. 1972). *See also, e.g., Ex parte Atkinson*, BPAI Appeal 2007-3900 ("optimization of a known result-effective variable in a given range is generally obvious only when it is reasonably expected that an improvement will arise in that range") (reversing Examiner's optimization-based obviousness rejection; internal citation omitted).

Applicants further note that the Court of Customs and Patent Appeals has held that the optimization of a parameter that is not recognized to be a result effective variable is an exception to the rule that it is a matter of obviousness for the skilled artisan to determine an optimum value within a disclosed range (*see In re Antonie*, 559 F.2d 618, 620 (C.C.P.A. 1977)) and respectfully assert that the Office Action does not adequately establish that the concentrations of IL-2 and IL-15 are art-recognized result-effective variables. Applicants further submit that even if IL-2 and IL-15 concentrations were established to be recognized as result effective within the art-disclosed ranges, it has not been shown that the claimed amounts of IL-2 and IL-15 would have been obvious in view of the ranges disclosed within the references.

Applicants also attach, for the Examiner's consideration, the declaration of Samuel Salot, an employee of Innate Pharma, S.A., that discusses a number of the assertions made in the previous Office Actions. As will be noted from the declaration, the argument that the cell number and the duration of cell culture would not be considered result-effective variables that one skilled in the art would have sought to optimize. Additionally, the declaration clearly indicates that the amounts of IL-2 recited in the currently claimed invention is far outside the range of IL-2 disclosed in any of the cited prior art references and, contrary to the arguments advanced in the Office Action, one skilled in the art would not have recognized that culturing T-cells in serum free medium and in the presence of IL-2 was a result effective variable that would have resulted in an increased percentage of γδ T-cells. Rather, one skilled in the art would have expected that culturing T-cells in serum free medium containing IL-2, at levels such as that claimed in this application, would have resulted in maximal proliferation having occurred with seven (7 days) after the T-cells were first cultured. A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). In this regard, Applicants note that the art cited in the Office Action tends to affirmatively teach away from the use of IL-2 in amounts greater than 50 U/ml. For example, Belmant *et al.* disclose that use of 50 U/ml of IL-2 and approximately 100 nM BrHPP gives greater than 66% Vdelta2+ (based on Fig.1), whereas Espinosa *et al.* appear to teach that 100 U/ml of IL-2 under very similar conditions gives only 55% Vdelta2+ (based on Fig. 4B, taking into account the logarithmic scale). Thus, one of skill in the art would not be motivated to further increase IL-2 concentrations

beyond the amounts disclosed in Belmant *et al.* since the teachings of Espinosa *et al.* would appear to indicate that culturing cells in the presence of higher levels of IL-2 results in less proliferation of γδ T-cells. Applicants also note that the teachings of Shea would tend to teach away from culturing cells for a period of more than seven days. As noted in the reference and declaration, expansion of T-cells did not occur beyond seven days. Applicants respectfully assert that the claimed invention is not obvious over the cited references and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 21, 23-25, 27-34, 51 and 52 are rejected under 35 U.S.C. § 103(a) as obvious over Espinosa *et al.* (2001), in view of Skea *et al.* (2001), Garcia *et al.* (1998) and Valeri (1976). The Office Action indicates that Espinosa *et al.* discovered BrHPP enabled immunostimulation of human gamma delta T lymphocytes. The Office Action further states that "Espinosa et al teach the concentration of the IL-2 to be 100 U/mL; however, while applicant specifically claims a cytokine concentration in the range of 150 U/mL to 500 U/mL, manipulation and optimization within this range would be well within the purview of one of ordinary skill in the art."

Applicants respectfully respond that each of the arguments presented above with respect to the rejection over Belmant *et al.* applies equally to the rejection over Espinosa in view of Skea *et al.* (2001), Garcia *et al.* (1998) and Valeri (1976). As discussed above, most, if not all, of the parameters such as cell number and the duration of cell culture would not be considered result-effective variables that one skilled in the art would have sought to optimize. Additionally, the amounts of IL-2 recited in the currently claimed invention for the proliferation of γδ-T-cells is far outside the range of IL-2 disclosed in any of the cited prior art references and, contrary to the arguments advanced in the Office Action, one skilled in the art would not have recognized that culturing T-cells in serum free medium and in the presence of IL-2 was a result-effective variable. Rather, one skilled in the art would have expected that culturing T-cells in serum free medium containing IL-2, at levels such as that claimed in this application, would have resulted in maximal proliferation having occurred within seven (7 days) after the T-cells were first cultured and that the use of IL-2 at levels higher than 50 U/mL would have resulted in reduced γδ T-cell proliferation in view of the teachings of the cited references. Thus, Applicants respectfully assert that the claimed

invention is not obvious over the cited references and reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/jb/sl
Attachment: Declaration of Samuel Salot